Appendix 2: Estimation of the parameters [posted as supplied by author]

Loss in (quality-adjusted) life-years

We used the most recent data from the Dutch national cancer registry.[1] For each tumour entity included in the analysis, we calculated the incidence rate per five-year age group as the total number of cancers diagnosed over the period 2000–2010 divided by the total number of person-years at risk among males in the Netherlands in the period 2000–2010. Background mortality was based on Dutch survival tables as of 2007 obtained from Statistics Netherlands.[2] Statistical uncertainty was included by assuming that the number of cancers diagnosed per five-year age group followed a Poisson distribution. The population-averaged risk $f_j(a;a_0=12)$ of having cancer *j* diagnosed at age *a* in a cohort of 12-year-old boys was obtained by multiplying the probability of survival from age $a_0=12$ years up to age *a* by the incidence rate of cancer at tumour site *j* in the corresponding age group. Lifetime risks were subsequently obtained by taking the sum of age-specific risks, yielding figures of 172, 74 and 305 per 100 000 men for penile, anal and oropharyngeal cancer, respectively.

Disease-specific survival $S_j(t)$ was estimated from observed cancer cases over the period 1999–2008, with male patients followed up through 2010.[1] Statistical uncertainty was included by assuming that the number of observed deaths occurring over each one-year interval followed a Poisson distribution. We fitted Cox proportional hazard models to adjust for age at cancer diagnosis, with three age groups: age <45 years, age between 45 and 74 years, and age 75+ years. The middle age group was the reference. Survival was relatively good for the youngest group and relatively poor for the oldest group. For the reference age group, conditional survival probabilities ten years after diagnosis were 0.65, 0.45 and 0.23 for penile, anal and oropharyngeal cancer, respectively.

We corrected the estimated survival functions $S_j(t)$ to account for the relatively favourable prognosis of HPV-positive cancer cases as compared with cases not related to HPV. Presence of HPV in penile cancers has been estimated to confer a hazard ratio of 0.21 (95% CrI: 0.06–0.76),[3] whereas a meta-analysis of HPV-specific survival in oropharyngeal carcinomas arrived at a hazard ratio of 0.46 (95% CrI: 0.37–0.57) relative to HPV-negative cases.[4] We adopted these hazard ratios as if the estimated survival functions applied to HPV-negative cases, which is acceptable as the majority of penile and oropharyngeal carcinomas are not related to HPV. Consequently, the corresponding ten-year survival probabilities improved to 0.91 (95% CrI: 0.72–0.97) and 0.50 (95% CrI: 0.42–0.58) for HPV-associated penile and oropharyngeal cancers, respectively.

Quality of life $U_j(t)$ was calculated per life-year after cancer *j* had been diagnosed. For each year since diagnosis, we estimated the fractions $q_j(t)$ of those still at risk of cancer-specific death and $r_j(t)$ of those recovered from cancer, with $q_j(t) + r_j(t) = S_j(t)$. We used quality of life valuations (i.e. utilities) that would apply to the majority of patients for the period starting after the primary treatment effects have resolved, which is of significant frequency and duration to be useful for modelling preventive interventions.[5] Utilities for the average patient surviving after the initial cancer diagnosis have been estimated at 0.79 (95% CrI: 0.74–0.84) for penile cancer, 0.57 (95% CrI: 0.52–0.62) for anal cancer, and 0.58 (95% CrI: 0.53–0.63) for oropharyngeal cancer, on a 0–1 scale relative to healthy individuals.[5] These values were derived from standard gamble questionnaires of non-cervical HPV-related cancers using preferences of the general population, which are well-suited for the use of utility as a measure for quality of life in cost-utility analysis.[6] We further assumed that quality of life for cancer survivors is equal to quality of life for those without cancer. Hence, the adjusted quality of life per life-year after cancer *j* has been diagnosed is:

$$U_j(t) = U_j \times \frac{q_j(t)}{S_j(t)} + \frac{r_j(t)}{S_j(t)}$$

HPV-attributable fractions

The proportion of cancer cases at site *j* that can be attributed to HPV type *i* is represented by p_{ij} in the model. Statistical uncertainty was incorporated by separately considering the fraction p_j of tumours at site *j* that can be attributed to HPV, and the relative contribution of types 16 and 18 among the HPV-positive cases. We only considered tumour specimen samples that tested positive for high-risk HPV DNA on the GP5+/6+ PCR enzyme immunoassay.[7] The HPV-attributable risk for penile cancer was estimated from 83 patients with invasive SCC treated at the Netherlands Cancer Institute between 1969 and 2000.[8] High-risk HPV DNA (either as a single or multiple infection) was detected in 30 cases,[9] yielding an HPV-attributable fraction of 0.36 (95% credible interval (CrI): 0.26–0.47). The HPV-attributable risk of oropharyngeal SCC was obtained from patients treated at the VU University Medical Centre. As we previously reported a significant increase in HPV positivity rate over the last two decades,[10] estimation of the etiologic fraction was restricted to the most recently obtained biopsies. Eighteen of the 62 patients that were treated for oropharyngeal SCC at the VU University Medical Centre during 2008–2011 tested positive for HPV, yielding an HPV-attributable fraction of 0.29 (95% CrI: 0.19–0.41). Note that the overall positivity rate over the period 1990–2010 was only 0.17.

Local tumour samples for estimating the HPV-attributable risk of anal cancer p_j were not available, hence the risk was estimated from a global meta-analysis.[11] We included only those studies that used GP5+/6+ primers, as choice of PCR was shown to have a significant effect on HPV detection rate. From the selected studies we derived an HPV-attributable fraction of 0.86 (95% CrI: 0.83–0.89) for anal carcinomas, irrespective of histological type. The relative contribution of types 16 and 18 among the HPV-positive cases was also obtained from published systematic reviews.[12–14] In addition, we corrected for possible differences between males and females in the etiologic fractions of both anal and oropharyngeal cancer. The association of anal cancer with HPV in Europe is smaller in men than in women, with an odds ratio (OR) of 0.29 (95% CrI: 0.19–0.44) for HPV

positivity of anal carcinomas in males verses females.[11] For oropharyngeal cancer we observed an increased HPV prevalence among men as compared to women, with an OR of 3.5 (95% CrI: 1.4–8.6).[10] With $\overline{p}_j$ denoting the etiologic fraction for tumour entity *j* in men and women combined, the corrected HPV-attributable risk for males p_j was obtained from the equation:

$$OR_j = \frac{p_j/(1-p_j)}{(2\overline{p}_j - p_j)/(1-2\overline{p}_j + p_j)}$$

Population attributable fractions related to MSM

The prevalence of MSM in the adult male population was obtained from a large-scale survey on sexual health and behaviour in the Netherlands, including over 2000 male respondents between 18–69 years of age.[15] We considered the proportion that identified themselves as homo- or bisexual (140 out of 2067) to be indicative of the prevalence of MSM in the general population, even though a somewhat higher proportion reported having had sex with another male in the past six months. To sufficiently capture uncertainty in the prevalence of MSM, we downsized the sample size tenfold and sampled *q* from a Beta(14, 193) distribution having expected value of 0.07 and a 95% CrI from 0.04 to 0.11.

Elevated cancer risks for MSM θ_j were obtained from a Danish population-based cohort study, where cancer patterns among men registered in homosexual partnerships were compared to those of the general population.[16] The study reported a relative risk of 31.2 (95% CrI: 8.4–79.8) for anal cancer among MSM versus heterosexual males. Relative risks of 2.5 (95% CrI: 1.1–5.8) and 5.6 (95% CrI: 0.6–20.2) were reported for carcinomas of the buccal cavity and pharynx, and for SCC of the tonsils, respectively. We pooled those figures to arrive at an estimate of 2.9 (95% CrI: 1.3–5.4) which we used as the relative risk for oropharyngeal cancers among MSM versus heterosexual males.

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